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Clinical Trial Paper

Clinical features and outcomes of interstitial lung disease in anti-Jo-1 positive antisynthetase syndrome

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ABSTRACT

Background: Interstitial lung disease (ILD) is a common extra-muscular manifestation of antisynthetase (AS) syndrome. ILD prevalence is higher with anti-Jo-1 antibody positivity. Data on long-term outcomes in these patients are lacking.
Methods: Over 15 years, we identified subjects with anti-Jo-1 positive AS syndrome and ILD. Demographics, pulmonary function testing (PFT), high-resolution computed tomography (HRCT), histopathology, and long-term survival were analyzed.
Results: We identified 103 subjects (mean age 49.2 years, female predominance [70%]). The predominant myopathy was polymyositis (64%) followed by dermatomyositis (24%). In approximately half of studied subjects, AS syndrome and ILD were diagnosed within 6 months of each other. The majority had restriction on PFTs (98%). Non-specific interstitial pneumonia (NSIP) was the most common HRCT pattern (52%), followed by NSIP overlapping with organizing pneumonia (OP) (22%). Thirty-nine subjects had biopsy data. Ten-year survival was 68%. Multivariable analysis adjusted for age at ILD diagnosis, gender, FVC and DLCO, revealed that male gender (HR = 2.60, p = 0.04) and DLCO at presentation (HR = 0.94, p = 0.05) significantly predicted mortality.
Conclusions: We present a large cohort of anti-Jo-1 positive AS syndrome with ILD and note good overall survival.

1. Introduction

Anti-synthetase syndrome (AS syndrome) is defined by the presence of autoimmune inflammatory myopathy [either polymyositis (PM), dermatomyositis (DM) or clinically amyopathic dermatomyositis (CADM)], interstitial lung disease (ILD), and positive serology for anti-aminoacyl-tRNA synthetase (antisynthetase ARS) antibodies [1–3]. Further, one or more of the following clinical features: arthritis, Raynaud's phenomenon and mechanic's hands, are also frequently observed in this syndrome [1–3].

ARS antibodies are directed against aminoacyl-transfer-RNA synthetases, a group of cytoplasmic enzymes that catalyze binding of amino acid groups to their cognate tRNA, a necessary step in the formation of polypeptides. To date, there are eight antibodies associated with AS syndrome. The first to be discovered and most commonly identified is anti-Jo-1, present in approximately 30% of cases [4]. Anti-Jo-1-antibody is directed against the cellular enzyme histidyl-tRNA synthetase [4,5].

ILD is the most common extra-muscular manifestation in AS syndrome with a prevalence ranging from 67% to 100% [3,6–10], higher than that reported in non-AS inflammatory myopathies which range from 20% to 75% [3,11–14]. In the presence of anti-Jo-1 positive serology, ILD appears more prevalent and carries with it a higher mortality. In a recent report by Aggarwal et al., ILD was the principal cause of death accounting for over 50% of observed mortality [15].

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While prior studies have reviewed the presenting clinical features of AS syndrome [10,16–18], little is known about anti-Jo-1 positive serology and severity of underlying ILD, response to treatment, and long-term survival. We reviewed all anti-Jo-1 antibody positive subjects with AS syndrome and associated ILD looking for predictors of disease progression and mortality.

2. Materials and methods

2.1. Study population and subject identification

Following approval by the Committee on Human Research at Mayo Clinic, Rochester, MN, we performed a retrospective cohort study reviewing the medical records of subjects with positive anti-Jo1-antibody and ILD seen at Mayo Clinic over a 15-year period (1995–2010). Criteria for AS syndrome in this study were: presence of positive Jo-1 anti-aminoacyl t-RNA (ARS) antibodies on serology, clinically diagnosed myopathic connective-tissue disease as determined by an expert rheumatologist (dermatomyositis, polymyositis, or overlap disease), and interstitial lung disease as defined by chest computed tomography (CT). Presence of associated clinical findings including arthritis, Raynaud's phenomenon, or mechanic's hands were collated but not used specifically to define the disease syndrome. Subjects with other identifiable causes for ILD, including other connective-tissue disease (CTD), medication related lung injury, environmental and occupational exposures, were excluded.

Demographics: Age, gender, underlying type of inflammatory myopathy, respiratory and rheumatologic symptoms, smoking history, gastroesophageal reflux disease, time since ILD diagnosis, characteristics of ILD findings, associated positive antibody serologies, and prior treatments and response to therapy were reviewed.

Pulmonary function tests (PFT): PFT data, including forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO) were abstracted at baseline and at serial follow-up. Disease progression on PFT was defined as decline in FVC by more than 10% of predicted, and/or decline in DLCO by more than 15% of predicted, similar to criteria established for idiopathic pulmonary fibrosis [19].

High Resolution CT chest: Chest CT images were reviewed at baseline and latest follow-up by two expert radiologists (DW and CWC) according to the 2013 American Thoracic Society classification of idiopathic interstitial pneumonias [20] as follows: usual interstitial pneumonia (UIP) pattern if the dominant abnormality was bilateral subpleural reticulation with lower lobe predominance and honeycombing with minimal or nonexistent ground glass opacities (GGO). Possible UIP was suggested by bibasilar and peripheral predominant reticular changes without specific honeycombing. Both UIP and possible UIP were grouped together for the purposes of this analysis. Nonspecific interstitial pneumonia (NSIP) pattern consisted of GGO and bilateral bibasilar reticulation with traction bronchiectasis and bronchiolectasis. An organizing pneumonia (OP) pattern consisted of patchy and/or migratory consolidation in a subpleural, peribronchial, or band-like pattern commonly associated with alternating ground-glass opacities. There was also an additional category of radiologic NSIP/OP overlap as previously described [21]. Those with radiologic features not fitting the above descriptions were labeled “atypical/unclassifiable.” ILD course assessed by CT was categorized as stable, improved, or progressing by serial CT assessment according to study radiologists’ interpretation [19]. If there were discrepancies between disease progression as measured by CT and PFT, we determined disease trend based on FVC findings. Progression of CTD was determined using rheumatology follow up assessment, and classified as improved, stable, or worsening in terms of extrapulmonary manifestations of AS syndrome.

Lung biopsy: When available, lung pathology was reviewed and categorized according to the 2013 American Thoracic Society/European Respiratory Society consensus statement in the following manner: UIP, NSIP, OP and diffuse alveolar damage [20]. An unclassified pattern was one that did not fit listed categories above. If a subject had discrepant findings on CT and biopsy, biopsy findings were taken to represent the underlying ILD pattern. Though transbronchial lung biopsies are not sufficient to diagnose or rule out a specific type of ILD, we included these biopsies when available. Our intention was to include all pathologic findings, recognizing that some transbronchial biopsies may have been performed to evaluate a superimposed acute infectious or inflammatory process.

2.2. Statistical analyses

Continuous data were expressed as mean (standard deviation) or median (interquartile range), as appropriate. Binary data were expressed as percentages. Predictors of disease progression or severity defined as worsening of radiologic and pulmonary function testing were evaluated using logistic and linear regression. A two-tailed p-value of <0.05 was considered statistically significant. Long-term all-cause mortality was assessed with Kaplan-Meier statistics using the Log rank method. Predictors of mortality were assessed using Cox proportional hazards analysis and a multivariate model was constructed with a priori adjustments for age, gender, FVC and DLCO. All statistical analysis was performed using JMP 10.1 (SAS Institute Inc., Cary, NC).

3. Results

Subject Characteristics: One hundred and three subjects with AS syndrome and positive anti-Jo-1 antibody over a 15-year period (1995–2010) were identified. There was noted female predominance (72/103, 70%) with a mean age of 49.5 (range 20.1–76.5) years at the time of ILD diagnosis. The most common underlying inflammatory myopathy was PM (66/103, 64%) followed by DM (25/103, 24%). Six subjects (6%) did not have myositis at presentation (Table 1).

In one-half of patients (52/103, 50%) CTD and ILD were diagnosed within 6 months of each other. In 16% of the cohort, ILD diagnosis preceded CTD diagnosis by over 6 months. Most subjects complained of dyspnea, cough, fatigue, and myalgia, with crackles noted on physical examination (Table 1). Raynaud's phenomenon and Mechanic's hands occurred in only 23% and 20% of subjects, respectively (Table 1). The majority of subjects were never smokers (60%).

Pulmonary function tests: Ninety-six subjects (93%) had available baseline PFT. The majority showed restriction (98%) with mean FVC at 65.7% and mean DLCO at 56.3% of predicted (Table 1). Follow-up PFT greater than 1 year after baseline was available in 56/96 (58%) subjects.

High Resolution CT chest: Eighty-five subjects (83%) had available baseline HRCT images that were reviewed by two independent radiologists. Seven additional subjects had radiological interpretations in the medical record, but no images available for review by the study radiologists. The most common pattern was NSIP ($n = 44$, 52%), followed by NSIP/OP ($n = 19$, 22%). Typical UIP pattern was not observed in any subject, with possible UIP pattern seen in 11 (13%) subjects. Fifty-five subjects had available follow-up HRCT chest images for review (Table 2).

Lung biopsy: Thirty-nine subjects (38%) had lung biopsy data, of which 30 (77%) were surgical and 9 (23%) were transbronchoscopic (Table 2). The most common histologic pattern was OP found in 10 subjects (26%) followed by NSIP in 9 (23%). UIP pattern was only

Table 1
Baseline characteristics of study subjects.

Characteristic	Result
Total subjects	103
Age at ILD Diagnosis, years [mean ± SD (range)]	49.5 ± 11.6 (20.1–76.5)
Age at CTD Diagnosis, years [mean ± SD (range)]	48.3 ± 12.3 (12.1–76.5)
Females (%)	72 (70)
Smoking Status, n (%)	
Current/Former smoker	41 (40)
Never smoker	62 (60)
Type of myositis[b], n (%)	
None	6 (6)
Dermatomyositis (DM)	26 (24)
Polymyositis (PM)	66 (64)
Overlap between DM, PM and/or other CTD	6 (6)
Months between CTD diagnosis and ILD diagnosis [median (IQR)][a]	0 (−1–14)
CTD and ILD diagnosed within 6 months of each other, n (%)	52 (50)
CTD diagnosed before ILD by ≥ 6 months, n (%)	36 (35)
ILD diagnosed before CTD by ≥ 6 months, n (%)	16 (15)
Clinical Features, n (%)	
Dyspnea	69 (67)
Cough	61 (59)
Fever	25 (24)
Fatigue	52 (50)
Rash	32 (31)
Arthritis/Joint Pain (non-erosive)	30 (29)
Raynaud's phenomenon	24 (23)
Myalgia or weakness	83 (81)
Gastroesophageal reflux disease	30 (29)
Crackles	80 (78)
Clubbing	2 (2)
Mechanic's hands	21 (20)
Initial anti-Jo-1 IgG antibody level, Units [median (interquartile range)]	137.9 (102.1–163.6)
Pulmonary function test parameters	
FEV_1, % pred, mean ± SD [range] (n = 92)	66.2 ± 17.5 [28–116]
FVC, % pred, mean ± SD [range] (n = 95)	65.7 ± 17.8 [25–116]
FEV1/FVC, mean ± SD [range] (n = 88)	83.5 ± 7.5 [61.7–119]
TLC, % pred, mean ± SD [range] (n = 74)	67.2 ± 14.7 [34–103]
DLCO, % pred, mean ± SD [range] (n = 89)	56.3 ± 21.9 [14–118]

ILD, interstitial lung disease; CTD; connective tissue disease; SD, standard deviation; FEV1, forced expiratory volume in the first second; FVC, forced expiratory volume; TLC, total lung capacity; DLCO, diffusing capacity of the lung for carbon monoxide.
[a] Negative values indicate that ILD was diagnosed before CTD.
[b] Percentages add up to more than 100% due to overlap of underlying disease types

seen in 6 subjects (15%), with diffuse alveolar damage (DAD) diagnosed in 5 (13%). An unclassifiable pattern was described in 4 subjects (10%). Other features such as chronic inflammation and respiratory bronchiolitis were seen but in conjunction with an identifiable interstitial pneumonia pattern (Table 2). Of the 6 subjects with UIP on pathology, the HRCT appearance was determined to be possible UIP, NSIP and NSIP/OP in two subjects apiece. Of the 9 subjects with NSIP pattern on biopsy, the HRCT appearance was determined to be NSIP in five subjects, possible UIP in two subjects, NSIP/OP in one subject, and one patient did not have radiological images for review.

Clinical Course of ILD and CTD: All subjects except one (102/103; 99%) received treatment. Clinical follow-up data was available in 91/102 (88%) subjects for CTD response and 90/103 (87%) subjects for ILD response to treatment. After a median follow-up of 9.5 (IQR 6.8–12.1) years, CTD improvement was noted in 11/91 (12%) subjects, while clinical stability was seen in 47 (52%) (Table 3). In contrast, improvement in ILD was noted in 10/90 (11%), while stability over the follow-up duration (either by PFT or HRCT) was seen in 32/90 (36%). All subjects except one received immunosuppressive therapy (102/103, 99%) with prednisone in addition to a variety of immunomodulating drugs (e.g. cyclophosphamide, methotrexate, azathioprine, mycophenolate mofetil, rituximab, amongst others). A median of 3 (interquartile range 2–3) drugs were used in each patient over a median duration of 60 (interquartile range 23–96) months. However, the overall response to treatment was not promising despite a combination of therapies (Table 3). Thirty-six (35%) subjects died during follow-up however, more than one-half of patients (54%) were still alive after 222.5 months (18.5 years) of longitudinal follow-up (Table 3 and Fig. 1). The 5- and 10-year survival in the cohort was 86% and 68%, respectively (Table 3). Where follow-up PFT was available, annual decline in FVC was associated with male gender, while annual decline in DLCO was associated with CT or biopsy appearance of UIP/possible UIP pattern (Table 4).

After performing multivariable analysis with a priori adjustment for age at ILD diagnosis, gender, FVC and DLCO, we found that male gender (HR = 2.60, 95% CI 1.05–6.09, p = 0.04) and DLCO at initial presentation (HR = 0.94, 95% CI 0.90–0.98, p = 0.05) were significant predictors of mortality. Detailed univariable and multivariable analyses are presented in Table 5.

Survival: Fig. 1 depicts the Kaplan-Meier survival curve for all subjects in our cohort. Fig. 2 suggests no difference in survival when the cohort was delineated by UIP vs non-UIP biopsy findings (Log rank p = 0.23; Wilcoxon p = 0.37). Fig. 3 suggests that survival for subjects who had a "possible UIP" pattern on HRCT was not significantly worse compared to subjects with ILD patterns inconsistent with UIP (Log rank p = 0.42, Wilcoxon p = 0.18).

Table 2
Features on imaging and pathology.

Characteristic	N (%)
HRCT – pattern at presentation (n = 85)	
- Possible UIP[a]	11 (13)
- NSIP	44 (52)
- NSIP/OP	19 (22)
- OP	3 (4)
- Atypical/Unclassifiable	8 (9)
HRCT – evidence of honeycombing (n = 85)	
- Present	1 (1)
- Absent	84 (99)
HRCT – predominance of findings (n = 85)	
- Upper lobes	0 (0)
- Lower lobes	82 (96)
- Diffuse	3 (4)
Pathologic findings on surgical lung biopsy (n = 30)[b]	
- UIP	6 (20)
- NSIP	9 (30)
- OP	6 (20)
- Non-specific fibrosis	1 (3)
- Chronic inflammation	4 (13)
- Diffuse alveolar damage	5 (25)
- Normal	1 (3)
Pathologic findings on bronchoscopic lung biopsy (n = 9)[b]	
- OP	4 (44)
- Respiratory bronchiolitis	1 (11)
- Non-specific fibrosis	3 (33)
- Chronic inflammation	6 (67)

HRCT, high-resolution computed tomography; UIP, usual interstitial pneumonia; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia.

[a] All HRCT patterns other than "possible UIP" were determined to be inconsistent with UIP (74/85, 87%).

[b] Several subjects had a combination of findings, and therefore, the percentages do not total up to 100.

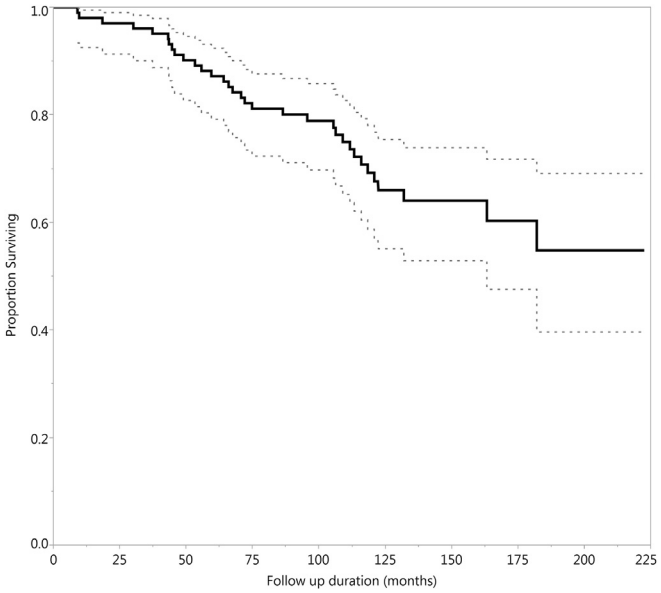

Fig. 1. Kaplan-Meier survival curve for the entire cohort. The curve shows that 5-year survival was 86%; 10-year survival was 68% and 54% survived at the end of maximum follow-up (222.5 months or 18.5 years). Dotted lines indicate the 95% confidence interval. ILD, interstitial lung disease.

4. Discussion

We describe a large single-center tertiary cohort of Jo-1 antibody positive AS syndrome with ILD [6,17,18,22–26]. Principal findings of our study include female predominance (70%), PM as the most commonly-associated inflammatory myopathy (63%), relative infrequency of mechanic's hands and Raynaud's phenomenon (23% and 20%, respectively), dominant NSIP pattern on HRCT (52%), and the association of male gender and initial DLCO with worse mortality.

Our cohort was similar in gender distribution to prior AS studies [16,18]. We found myositis and ILD typically coexisted at the time of diagnosis or shortly after as described in prior studies [6,10,18]. We noted lower rates of mechanic's hands and Raynaud's syndrome compared to the report by Marie et al. [10], but similar rates of mechanic's hands as described by other series [6,17,18]. Level of anti-Jo1 serum titers did not correlate with presenting pulmonary function, radiologic, or pathologic features. Titer levels also did not

Table 3
Treatment and clinical course of the entire cohort.[a]

Characteristic	Result
Number of Drugs Used for Treatment, median (IQR) [range]	3 (2–3) [0–6]
Duration of Treatment in months, median (IQR) [range][a]	60 (23–96) [3–288]
Response of CTD to Treatment, n (%)[a] [n = 91]	
Improved	11/91 (12%)
Stable	47/91 (52%)
Worsened	33/91 (36%)
Unknown	12
Response of ILD to Treatment, n (%)[a] [n = 90]	
Improved	10/90 (11)
Stable	32/90 (36)
Worsened	48/90 (53)
Unknown	13
FVC change (%/year) [median (IQR)] [n = 64]	−0.3 (−2.1–1.9)
DLCO change (%/year) [median (IQR)] [n = 56]	−0.5 (−2.6–1.7)
Treated with immunosuppressive therapy, n (%)	102 (99)
Died during follow-up, n (%)	36 (35)
5-year survival, n (%)	89 (86)
10-year survival, n (%)	70 (68)
Survival at maximum follow-up (222.5 months), n (%)	56 (54)

IQR, interquartile range; CTD; connective tissue disease; ILD, interstitial lung disease; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide.

[a] In the total cohort of 103 subjects, 102 (99%) received immunosuppressive therapy. Of these 103 subjects, 91 (88%) had follow-up data available for CTD response, and 90 (87%) had follow-up data available for ILD response. Duration of treatment was documented in the clinical notes in 82 subjects.

Table 4
Association of diagnostic findings and clinical response with changes in PFT parameters.

Parameter	FVC change (%/year)	P value	DLCO change (%/year)	P value
Gender:				
Male	−1.7 (−3.8, 0.7)	**0.03**	−0.8 (−4.6, 1.4)	0.46
Female	0.03 (−1.7, 3.7)	(ref)	−0.3 (−2.2, 2.1)	(ref)
Smoking status:				
Ever smoker	−1.1 (−2.6, 1.7)	0.14	0.0 (−2.6, 2.2)	0.46
Never smoker	−0.04 (−1.9, 1.9)	(ref)	−0.9 (−2.6, 1.3)	(ref)
HRCT features				
Possible UIP	−0.4 (−4.0, 1.9)	0.75	−1.8 (−5.1, −0.7)	0.09
Inconsistent with UIP	−0.1 (−2.1, 1.9)	(ref)	−0.2 (−2.2, 1.8)	(ref)
Biopsy:				
UIP	−2.4 (−4.9, 1.9)	0.47	−5.3 (−7.8, −2.8)	0.08
Not UIP	−0.1 (−2.1, 1.7)	(ref)	−0.1 (−1.0, 0.8)	(ref)
CT or Biopsy:				
UIP/Possible UIP	−0.4 (−3.0, 2.0)	0.78	−2.3 (−7.1, −0.9)	**0.03**
Inconsistent with UIP	−0.1 (−2.1, 1.7)	(ref)	−0.2 (−2.1, 1.8)	(ref)
Response to therapy:				
Worsening of ILD	−1.5 (−2.5, 1.3)	0.24	−0.8 (−3.4, 0.3)	0.42
No worsening of ILD	0.03 (−1.7, 2.1)	(ref)	−0.3 (−2.3, 2.1)	(ref)
Worsening CTD	−1.5 (−2.5, 1.3)	0.24	−0.8 (−3.4, 0.3)	0.42
No worsening of CTD	0.03 (−1.7, 2.1)	(ref)	−0.3 (−2.3, 2.1)	(ref)

FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide; HRCT, high-resolution computed tomography; UIP, usual interstial pneumonia; ILD, interstitial lung disease; CTD, collagen vascular disease.
Figures indicate median (interquartile ranges); all comparisons are using the Wilcoxon rank sum test.
Negative values indicate a decline over time. Follow-up data were available in 56/103 (54%) patients for DLCO and 64/103 (62%) patients for FVC.
Bolded values are those that are statistically significant, defined by P values <0.05.

Table 5
Univariate and multivariate analysis of predictors of mortality.

	Univariate hazard ratio (95% CI)	P value	Multivariate hazard ratio (95% CI)	P value
Clinical parameters:				
Age at CTD Diagnosis	1.06 (1.03–1.09)	<**0.0001**	1.03 (0.99–1.07)	0.17
Age at ILD Diagnosis	1.07 (1.03–1.10)	<**0.0001**	1.04 (0.99–1.08)	0.10
Gender, Male	1.28 (0.60–2.60)	0.51	2.60 (1.05–6.09)	**0.04**
Smoking (ever)	1.86 (0.94–3.72)	0.08	1.10 (0.46–2.63)	0.83
Mechanic's Hands	0.88 (0.33–1.99)	0.77	0.96 (0.27–2.69)	0.94
Myalgia/Weakness	0.99 (0.45–2.50)	0.99	1.99 (0.74–6.06)	0.18
Raynaud's Phenomenon	0.90 (0.36–1.96)	0.80	1.51 (0.42–4.68)	0.50
GERD	0.46 (0.17–1.05)	0.07	0.78 (0.25–2.03)	0.62
Anti-Jo-1 antibody level	1.00 (0.99–1.01)	0.85	1.00 (0.99–1.01)	0.94
Pulmonary function:				
Initial $FEV_{1,}$ % predicted	0.95 (0.93–0.98)	<**0.0001**	0.99 (0.93–1.08)	0.87
Initial FVC, % predicted	0.94 (0.92–0.96)	<**0.0001**	0.99 (0.95–1.02)	0.51
Initial DLCO, % predicted	0.94 (0.91–0.97)	<**0.0001**	0.94 (0.90–0.98)	**0.005**
Initial TLC, % predicted	0.95 (0.92–0.98)	**0.0003**	1.01 (0.95–1.06)	0.63
Radiologic/pathologic findings:				
Possible UIP on initial HRCT	1.55 (0.45–4.07)	0.45	1.66 (0.25–6.27)	0.54
UIP pattern on pathology	1.89 (0.60–5.10)	0.26	1.90 (0.51–6.47)	0.32
Possible UIP pattern on HRCT or UIP on pathology	2.25 (0.93–4.93)	0.07	2.01 (0.70–5.11)	0.18
Response to therapy:				
Worsening of CTD	2.25 (1.06–4.77)	**0.036**	1.76 (0.65–4.68)	0.26
Worsening of ILD	3.03 (1.34–7.74)	**0.007**	1.20 (0.41–3.71)	0.74

Multivariate analysis was performed using Cox proportional hazards with adjustment for variables selected a priori (age at ILD diagnosis, gender, FVC% and DLCO%). For "age at CTD diagnosis," the "age at ILD diagnosis" was substituted in the model.
CI, confidence interval; CTD, collagen vascular disease; ILD, interstitial lung disease; GERD, gastroesophageal reflux disease; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide; UIP, usual interstitial pneumonia; HRCT, high-resolution computed tomography.
Bolded values are those that are statistically significant, defined by P values <0.05.

predict response to therapy or survival from an ILD or CTD perspective. This is in contrast to a prior study by Stone et al. [17] who noted correlation of quantified anti-Jo-1 antibody levels with several domains of organ specific disease activity as measured by a standardized visual analog scale. They noted correlation with pulmonary symptoms in a smaller longitudinal subset while no particular cut-offs supported more advanced or progressive radiologic or clinical findings in our study.

The most common radiologic pattern found in our cohort was NSIP, a finding similarly described in the literature in association with other AS syndrome and the inflammatory myopathies [11,18,25,27,28]. A prior study by Yousem et al. suggested UIP CT pattern to be more common, however, the studied antibody was anti-PL-7 ARS with a sample size of only 8 subjects [29]. While NSIP CT pattern may be recognized as such, it is well known that NSIP is a pathologic diagnosis and any survival advantage in this cohort may be attributable as well to the improved overall survival of pathologic UIP when associated with connective-tissue disease. In our cohort, possible UIP CT pattern was not frequent (13%) and not associated with higher mortality risk when compared to subjects with other radiologic features. Median survival with a possible UIP pattern on HRCT was over 10 years, and with a UIP pattern on

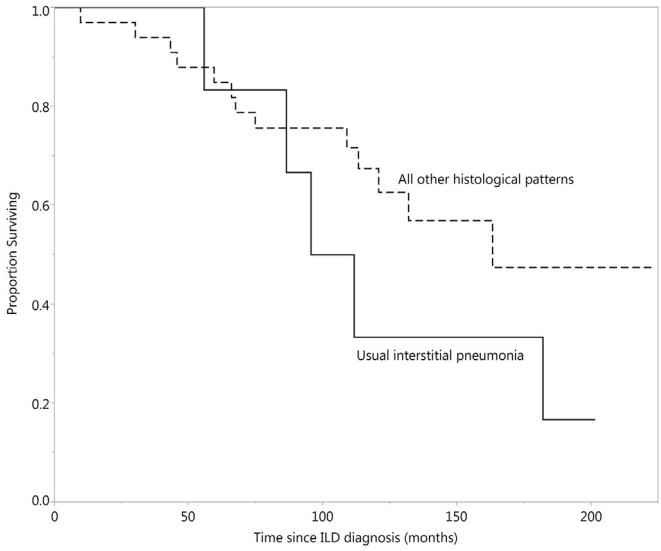

Fig. 2. Kaplan-Meier survival curve grouped on the basis of lung biopsy findings (N = 39) into usual interstitial pneumonia (UIP) (solid line) and all other histological patterns (dashed line). Median survival was 103.6 months for UIP versus 163.2 months for other histological patterns (Log-rank p = 0.23, Wilcoxon p = 0.37). ILD, interstitial lung disease.

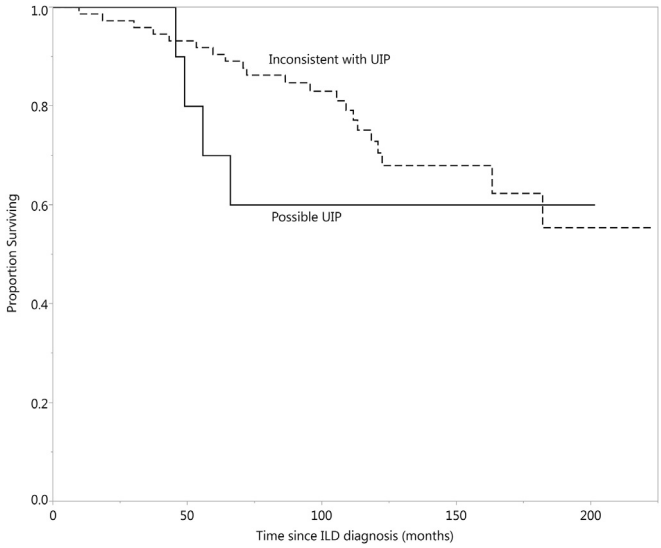

Fig. 3. Kaplan-Meier survival curve grouped on the basis of high-resolution computed tomography (HRCT) findings into possible usual interstitial pneumonia (UIP) pattern (solid line) and all other HRCT patterns inconsistent with UIP (dashed line). Median survival was not significantly different between groups (Log-rank p = 0.42, Wilcoxon p = 0.18). ILD, interstitial lung disease.

biopsy 8.6 years, both of which are significantly better than radiologic or histologic UIP pattern associated with idiopathic pulmonary fibrosis [30].

In our cohort, thirty-nine subjects underwent surgical or bronchoscopic lung biopsy, primarily because of atypically presenting CT or clinical features initially non-diagnostic of AS disease. The most common histologic pattern was OP (n = 10, 26%), followed by NSIP, perhaps because subjects with UIP HRCT pattern were less likely to be referred for biopsy. NSIP as a predominant histologic finding is concordant with other studies [16,18]. Pathologic features of UIP were not associated with increased mortality when found with AS, perhaps more likely reflecting a lack of power given the low number of subjects with UIP histology and possible UIP CT pattern that underwent biopsy.

Despite subjects having received a number of immunosuppressive drugs, a large proportion had clinical and/or PFT decline when follow-up was assessed. Our study provides the first data on long-term outcomes with directed management in AS syndrome. Currently there are no evidence-based recommendations to guide treatment as reflected by the wide array of medication treatment strategies used in our cohort. One of the significant challenges to establishing evidence-based recommendations remains the rarity of AS syndrome itself. No difference in survival was noted among different drug types and their combinations, or duration of therapy with no subject undergoing lung transplantation. Again, stability or improvement of CTD was achieved with treatment in about 64% of subjects, with radiologic ILD findings stabilizing or improving in about 46%. Collaborative clinical trials will be needed to identify the most effective modality of medical management, though we highlight the overall better survival when compared to idiopathic fibrotic lung diseases.

Factors associated with disease progression and predictors of early mortality in our cohort were male gender, and low initial DLCO. While a UIP pattern on CT was associated with more rapid deterioration in a study by Marie et al. [10], our study did not suggest a similar relationship. The proportion of current or former smokers was higher than national averages (40%), and cigarette smoking was associated with a trend towards reduced survival on univariable analysis in our study. Again, general recommendation for smoking cessation is emphasized in patients with AS syndrome.

Our study has several limitations. First, it is a single-center retrospective cohort analysis consisting exclusively of subjects referred to an ILD-focused practice, and may not be representative of a larger AS population. Second, our cohort included only AS patients with ILD, therefore we did not assess the prevalence of ILD overall in all subjects with AS syndrome. Third, we did not assess the prevalence of pulmonary hypertension within our cohort, and having this data would have further added to our understanding of ILD associated with AS syndrome and its contribution to survival. Finally, our study focused on patients with anti-Jo-1 positive AS syndrome making our results less generalizable to AS syndrome associated with other autoantibodies. Due to the retrospective nature of our study, follow-up testing with CT or PFTs was not available in all patients or obtained at fixed intervals. However, ours is the largest descriptive report of Jo-1 positive AS syndrome to date with a robust number of biopsied patients and a maximum follow-up of 18.5 years. We have also, for the first time, identified several factors associated with poorer outcome in patients with anti-Jo-1 positive AS syndrome ILD.

In conclusion, we present a large single-center cohort of AS syndrome-associated ILD with anti-Jo-1 antibody positivity, highlighting the relative rarity of mechanic's hands and Raynaud's phenomenon, the predominance of NSIP and OP among biopsied patients, and relatively good survival (more than half alive at 18.5 years of longest follow-up), with increased risk of mortality driven mostly by male gender and low DLCO at presentation.

Conflict of interest statement

None of the authors have any relevant conflicts of interest to disclose.

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Take home message:

Subjects with anti-Jo-1 positive antisynthetase syndrome-associated ILD usually have NSIP and median survival >18 years.

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